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Macrophages and hypoxia in human chronic kidney disease

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Chronic kidney disease is characterized by progressive interstitial fibrosis, reduced blood flow, and tubular atrophy, which present a common pathway of destruction irrespective of the initial underlying pathology. There is comprehensive evidence that the interactions of infiltrating macrophages with resident tissue cells play a critical role in this process. A new study now describes the correlation between macrophages, capillary density, and interstitial scarring and suggests distinct differences in early and advanced renal disease.

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Renal disease has a wide spectrum of histological patterns, suggesting a variety of immunopathogenetic mechanisms of injury. Not all renal diseases lead to end-stage renal failure, but those that do are characterized by progressive renal scarring. Macrophages have been extensively studied in this context and play an important role in the initiation and progression of renal fibrosis.[1] Progressive tubulointerstitial disease is associated with loss of interstitial capillaries and reduced blood flow, which suggests that the renal cortex becomes more ischemic as chronic kidney disease evolves.

A new study by Eardley *et al.*[2] (this issue) examines the relationship between hypoxia and inflammation in chronic kidney disease. This study investigates whether there is a clinical correlation between interstitial capillary density, macrophage numbers, albuminuria, and monocyte chemoattractant protein-1 (MCP-1)/CCL2 urinary excretion in renal biopsies of patients with early and advanced renal disease. The main finding of the study is that in patients with limited renal scarring there was a strong association between capillary density, macrophage infiltration, and chronic damage but no correlation between capillary density and macrophage numbers. In keeping with the group's previous work,[3] there was, however, a strong association of albuminuria with macrophage numbers (and MCP-1/CCL2 levels), which suggests that this is an important mechanism for macrophage recruitment in patients with limited disease.

In contrast, in patients with more severe scarring there was a strong correlation between capillary density, macrophage numbers, and chronic damage but no association between capillary density and MCP-1/CCL2, which suggests that the dominant pathway for macrophage recruitment and proliferation in this setting is MCP-1/CCL2 independent.

A small number of studies in experimental models have previously demonstrated an association between tubulointerstitial hypoxia and progressive injury[4] despite the obvious difficulties of quantifying tissue oxygenation at the cellular level. In the new study by Eardley *et al.*[2] (which used biopsies from patients with chronic kidney disease), hypoxia cannot be assessed directly, but the authors provide strands of evidence that suggest worsening interstitial hypoxia in advanced disease. This is achieved by immunohistochemistry to assess capillary density combined with validated indirect markers of tissue hypoxia such as vascular endothelial growth factor, a hypoxia-induced angiogenic factor, and carbonic anhydrase IX, a transmembrane glycoprotein that is hypoxia inducible. Despite the need to detect tissue hypoxia *in vivo*, there are few methods available, and most studies examining renal tissue have relied on chemical tools such as pimonidazole, which is also extensively used to detect hypoxic tumor cells *in vivo*.[5] More complex approaches, such as a hypoxia-sensing transgenic rat,[4] and imaging techniques, such as blood oxygen level-dependent magnetic resonance imaging,[6] have been used and offer scope for future development. Hypoxia, as is mentioned above, can also be assessed indirectly by detection of the large number of genes that are upregulated in response to hypoxia. The family of hypoxia-inducible transcription factors (HIF), the most extensively studied, is upregulated in the kidney in response to hypoxia, and pharmacological HIF stabilization has been shown to confer tissue protection in experimental models.[7] Systems biology approaches may prove highly useful to identify other genes that are upregulated in renal hypoxia and, possibly more importantly, to identify genes that are repressed in hypoxic conditions, and the inhibition of certain gene products may ultimately turn out to be critical for the progression of renal injury in hypoxic conditions.

The study by Eardley *et al.*[2] is observational and associative, but nevertheless significant for our understanding of the evolution of renal injury. Hypoxic damage secondary to obliteration of the interstitial capillary bed may represent an important pathway in human chronic kidney disease for the recruitment and *in situ* retention and proliferation of macrophages, the dominant infiltrating cell in the progression of chronic kidney disease.

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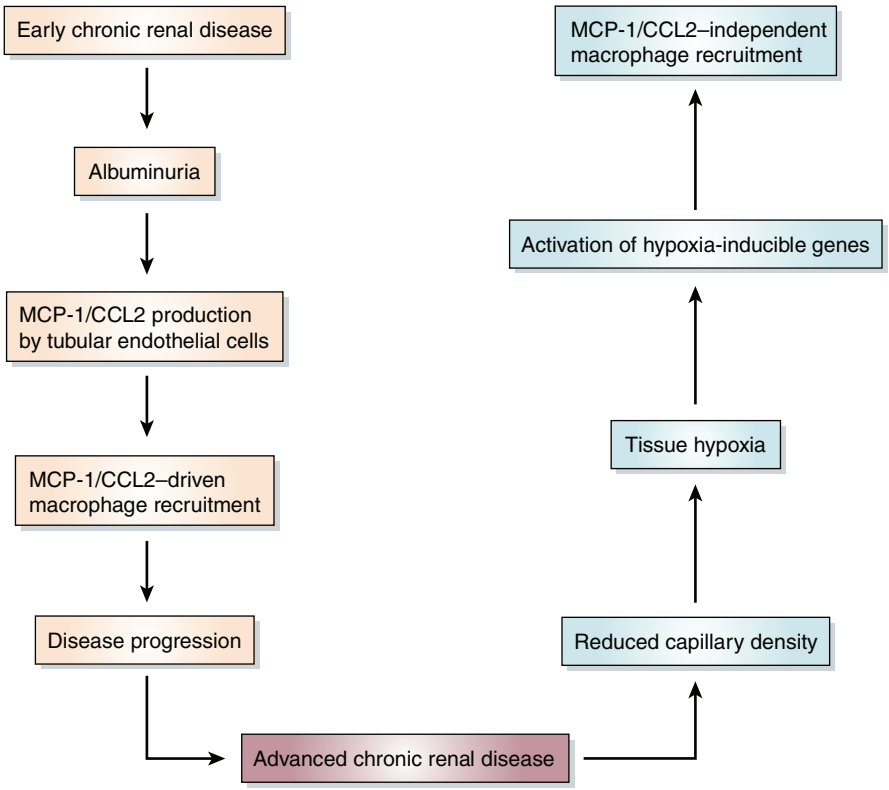

Figure 1 | The mechanism responsible for tissue damage in tubulointerstitial disease. In early renal disease, albuminuria induces monocyte chemoattractant protein-1 (MCP-1)/CCL2 production by tubular endothelial cells, which in turn drives recruitment of proinflammatory macrophages. Disease progression leads to rarefaction of capillaries, tissue hypoxia, and activation of hypoxia-inducible genes, which then drive macrophage recruitment independent of MCP-1. These macrophages may, depending on their properties, lead to further disease progression or partial restoration of normal function.

Oxygen consumption by macrophages may exacerbate hypoxia, whereas the multitude of secretory molecules induced in macrophages encountering hypoxic conditions may contribute to cell survival. This study, in conjunction with the overwhelming evidence from experimental models showing that macrophages within the inflamed kidney are heterogeneous depending on the mode of recruitment and the microenvironment they encounter,[8,9] raises important questions. What are the chemotactic factors that drive macrophage recruitment in advanced disease, and what are the functional properties of macrophages that have been recruited through chemotactic factors other than MCP-1 (in comparison with those that have infiltrated the kidney early in the disease process in response to MCP-1)? Furthermore, the analysis of macrophage properties in limited versus advanced disease and, possibly more importantly, of macrophages in areas of severe versus mild capillary loss in advanced disease should identify biomarkers that may help predict the progression of the underlying disease process.

Proteinuria, hypoxia, and the functional properties of macrophages infiltrating the kidney in chronic disease are critical for the outcome of the disease process, and one strength of the paper by Eardley *et al.*[2] is that these have not been studied in isolation. This enabled the authors to speculate that the patchy nature of early disease, where macrophages localize to affected nephrons, is a consequence of localized increased production of MCP-1/CCL2 produced by tubular epithelial cells in response to albumin and other glomerular filtered proteins. They further suggest that in advanced disease, when nephron segments become scarred, ischemia becomes a dominant factor in further promoting macrophage infiltration and proliferation at these sites. These local processes will then involve bystander nephrons, with the development of both primary and secondary proteinuria and ischemia (Figure 1). This raises the question of whether proteinuria, even though it remains a surrogate marker for disease progression, may be of less pathogenic relevance in late disease. Before we can elucidate these important questions, better tools to assess tissue hypoxia and its effects on different renal cell types, particularly macrophages, are urgently needed. Nevertheless, once we have a better understanding of the effects of hypoxia and proteinuria on macrophage function, it is not inconceivable that the functional properties of macrophages in biopsies of patients with chronic kidney disease will provide important information to predict outcome and aid therapeutic decisions.

DISCLOSURE

The author declared no competing interests.

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